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Preventing Osteoporosis-Related Fractures: An Overview

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ABSTRACT

Osteoporosis is a skeletal disorder characterized by compromised bone strength, which predisposes a person to increased risk of fracture. In the United States, 26% of women aged ≥65 years and >50% of women aged ≥85 years have osteoporosis. Over 1.5 million fractures per year are attributable to osteoporosis; these fractures result in 500,000 hospitalizations, 800,000 emergency room visits, 2.6 million physician visits, 180,000 nursing home placements, and $12 billion to $18 billion in direct healthcare costs each year. Fracture also results in loss of function and has a negative impact on psychological status. In recognition of the importance of bone health, the US Surgeon General has, for the first time, issued a comprehensive report on bone health and treatment. The report recommends a pyramidal approach to osteoporosis treatment that includes calcium and vitamin D supplementation, physical activity, and fall prevention as the first line in fracture prevention. The second level consists of treating secondary causes of osteoporosis; the third and top level consists of pharmacotherapy. Pharmacotherapeutic interventions (e.g., bisphosphonates, selective estrogen receptor modulators, calcitonin, and teriparatide) in women with postmenopausal osteoporosis provide substantial reduction in fracture risk over and above risk reduction with calcium and vitamin D supplementation alone. Despite the effectiveness of therapy, most patients who receive treatment do not remain on treatment for >1 year. An important approach to reducing the rate of fractures is first to target our treatments to patients at high risk for fracture and then to develop strategies to improve treatment continuation rates.

KEYWORDS: Bone loss; Calcium/vitamin D supplementation; Fractures; Menopause; Osteoporosis; Pharmacotherapeutic intervention

Osteoporosis is a skeletal disorder characterized by impaired bone strength that increases the risk of fracture. Bone strength is a composite of bone density and bone quality. The latter is not fully understood but includes aspects of bone architecture, damage accumulation (e.g., microfractures), and mineralization.[1]

In the United States alone, osteoporosis affects >10 million individuals aged ≥50 years; an additional 33.6 million have low bone mass (osteopenia) and are potentially at risk for osteoporosis and its complications.[2] Because bone loss is positively associated with age, the prevalence of osteoporosis increases from 19% among women aged 65 to 74 years to >50% in women aged ≥85 years. As a result of the aging of the population, the number of people aged ≥50 years with osteoporosis is expected to increase to 12 million by 2010 and to nearly 14 million by 2020.[2]

Osteoporosis is considered a "silent disease" until a fracture occurs.[3] Approximately 1.5 million fractures per year are attributable to osteoporosis. Among white women aged ≥50 years, approximately 40% will experience a hip, spine, or wrist fracture during the remainder of their lives.[2] In the United States alone, osteoporotic fractures are responsible for approximately 500,000 hospitalizations, 800,000 emergency room visits, 2.6 million physician visits, and 180,000 nursing home placements each year.[2] Costs related to osteoporosis are high: in 2002, direct care expenditures for osteoporotic fractures ranged from $12 billion to $18 billion. Indirect costs, primarily from lost productivity, add substantially to the total cost of care for fracture. These costs are projected to double or triple over the next few

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decades, in parallel with the increasing prevalence of osteoporosis.[2]

Hip and vertebral fractures are the most important types of fracture. Hip fractures are associated with substantially increased risk of institutionalization and death.[4] Vertebral fractures are associated with chronic back pain, spinal deformity, functional limitations, and increased risk of hospitalization and mortality.[5–7] Many who have a vertebral fracture experience significant pain and height loss, and may lose the ability to perform normal activities of daily living, which may have in a negative impact on self-esteem, body image, and mood.[1]

NATURAL HISTORY AND EVOLUTIONARY PERSPECTIVE

Osteoporosis is characterized by bone loss and changes in bone structure. The process of bone loss and bone formation is mediated at the cellular level by osteoclasts on one hand, which act to remove old bone, and osteoblasts on the other, which are involved in bone formation. An equilibrium between these 2 processes is maintained in young, healthy women; however, the balance shifts toward resorption after menopause and worsens over time. As a result, bone is not replaced and becomes fragile, increasing the risk of fracture.

One hypothesis for the rapid shift toward bone resorption in recently postmenopausal women is the rapid reduction in estrogen levels. Jarvinen and colleagues[8] have speculated that the increase in estrogen in girls during puberty drives calcium reserve accumulation. This "reproductive safety deposit" provides a store from which calcium can be released during pregnancy and lactation. Loss of estrogen at menopause results in net resorption of the calcium reserve because it is no longer necessary to support reproduction.

CLINICAL RISK FACTORS FOR FRACTURE

A number of risk factors have been identified for osteoporotic fracture (**Table 1**).[9] Strong risk factors for fracture include prior fragility fracture, low estrogen levels, premature menopause, long-term secondary amenorrhea, glucocorticoid therapy (prednisone >7.5 mg/day [or equivalent] for ≥6 months), maternal history of hip fracture, and low body mass index. Sedative treatment, visual impairment, and reduced mobility—all risk factors for falling—predict fracture in older, but not in younger, patients. Smoking, alcohol, and poor calcium intake are also linked to fracture risk.[9]

DIAGNOSIS OF OSTEOPOROSIS

The severity of bone loss is categorized relative to mean bone mineral density (BMD) in young, healthy women. A 1-unit change in T-score corresponds to a 1 standard deviation difference from the reference population. World Health Organization (WHO) operational definitions for osteoporosis and osteopenia are shown in **Table 2**.[10]

Table 1 Risk factors for osteoporotic fractures in women

- Age
- Premature menopause
- Primary amenorrhea or amenorrhea associated with low estrogen
- Asian or white ethnic origin
- Previous fragility fracture
- Low bone mineral density
- Glucocorticoid therapy
- High bone turnover
- Family history of hip fracture
- Poor visual acuity
- Low body weight
- Neuromuscular disorders
- Cigarette smoking
- Excessive alcohol consumption
- Long-term immobilization
- Low dietary calcium intake
- Vitamin D deficiency

Adapted with permission from *Lancet*.[9]

Measurement of bone mass is used to determine severity of bone loss and fracture risk and to distinguish patients with osteoporosis from those with osteopenia and normal bone density. Most guidelines recommend dual x-ray absorptiometry (DXA) as the preferred technique for measurement of BMD.[3,11,12]

GUIDELINES FOR MANAGEMENT OF OSTEOPOROSIS

The American Association of Clinical Endocrinologists (AACE), North American Menopause Society (NAMS), and National Osteoporosis Foundation (NOF) provide recommendations for the identification of patients in need of therapy (**Table 3**).[3,11,12] According to AACE guidelines, all women aged ≥65 years, women ≥40 years with a history of fracture not caused by severe trauma, and younger peri- and postmenopausal women who have clinical risk factors for fractures should be assessed for osteoporosis.[12]

The AACE guidelines identify 3 categories of women who may benefit from pharmacologic treatment: women with postmenopausal osteoporosis (e.g., those with low-trauma fracture or low BMD), women with borderline-low BMD (T-scores ≤1.5) if risk factors are present, and women in whom nonpharmacologic therapy has been demonstrated to be inadequate for preventing bone loss or fracture.[12]

NAMS recommends that BMD be measured in all women with medical causes of bone loss, in all patients ≥65 years regardless of the presence of additional risk factors, and in younger postmenopausal women with ≥1 risk factor. Measurement of BMD at the total hip is preferred in women aged ≥60 years because spinal measurements may be unreliable in older patients. Spine BMD testing may be more useful in younger postmenopausal women for 2 reasons: (1) There are fewer degenerative spine changes in younger

Table 2 World Health Organization (WHO) definition of osteoporosis

Diagnostic Category	T-score	Bone Mineral Density
Normal	>−1	Within 1 SD of a young normal adult
Low bone mass	−1 to −2.5	Between 1 and 2.5 SD below that of a young normal adult
Osteoporosis	<−2.5	>2.5 SD below that of a young normal adult
Severe osteoporosis	<−2.5 and ≥1 fragility fracture	>2.5 SD below that of a young normal adult

Adapted from WHO Technical Report Series.[10]

Table 3 Guidelines for the identification of patients management for postmenopausal osteoporosis

	National Osteoporosis Foundation	North American Menopause Society	American Association of Clinical Endocrinologists
Who should receive BMD testing?	• All women aged ≥65 yr • Younger postmenopausal women with ≥1 risk factor • Postmenopausal women who present with fractures (to confirm diagnosis and determine disease severity)	• All women aged ≥65 yr • All women with medical causes of bone loss • Younger postmenopausal women with ≥1 risk factor	• All women aged ≥65 yr • All women aged ≥40 yr who have sustained a fracture unrelated to major trauma • All peri- and postmenopausal women who have risk factors for fractures or bone loss
Who should receive treatment?	• Women with BMD T-scores <−2.0 by hip DXA with no risk factors • Women with BMD T-scores <−1.5 by hip DXA with ≥1 risk factor • Women with a prior vertebral or hip fracture	• Postmenopausal women with total hip or spine T-scores <−2.5 • Postmenopausal women with total hip or spine T-scores from −2.0 to −2.5 and ≥1 risk factor for fracture • All postmenopausal women with osteoporotic vertebral fracture (no BMD needed)	• Women with low-trauma fracture and low BMD • Women with BMD T-scores ≤−2.5 • Women with borderline-low BMD (T-score ≤−1.5) with risk factors • Women in whom nonpharmacologic measures are ineffective

BMD = bone mineral density; DXA = dual x-ray absorptiometry.
Adapted from National Osteoporosis Foundation,[3] *Menopause*,[11] and *Endocr Pract.*[12]

women and (2) bone loss is generally faster in the spine than in the hip and thus allows earlier detection of osteoporosis.[11]

The NAMS guidelines are somewhat more conservative than the AACE guidelines in identifying patients who require treatment. Treatment is recommended in all postmenopausal women with prior vertebral or hip fracture or with total hip or spine T-scores <-2.5 and in postmenopausal women with total hip or spine T-scores from -2.0 to -2.5 and ≥ 1 additional risk factor.[11,12]

The NOF recommends BMD testing in women aged ≥65 years regardless of risk factors, younger postmenopausal women with ≥1 risk factor, and all postmenopausal women with fracture. Therapy should be initiated in women with T-scores <-2.0 by hip DXA with no risk factors, those with T-scores <-1.5 and ≥ 1 risk factor, and all patients with a prior vertebral or hip fracture.[3]

OVERVIEW: TREATMENT OF BONE DISEASE

Osteoporosis responds to treatment. In addition to lifestyle changes such as improved diet and increased exercise, there are a number of effective, well-tolerated therapies that may dramatically reduce patients' risk of fracture. There are 4 major goals in the treatment of osteoporosis: prevention of fracture; stabilization or achievement of increased bone mass; relieving symptoms of fractures and skeletal deformity; and maximizing physical function.[12] To achieve these

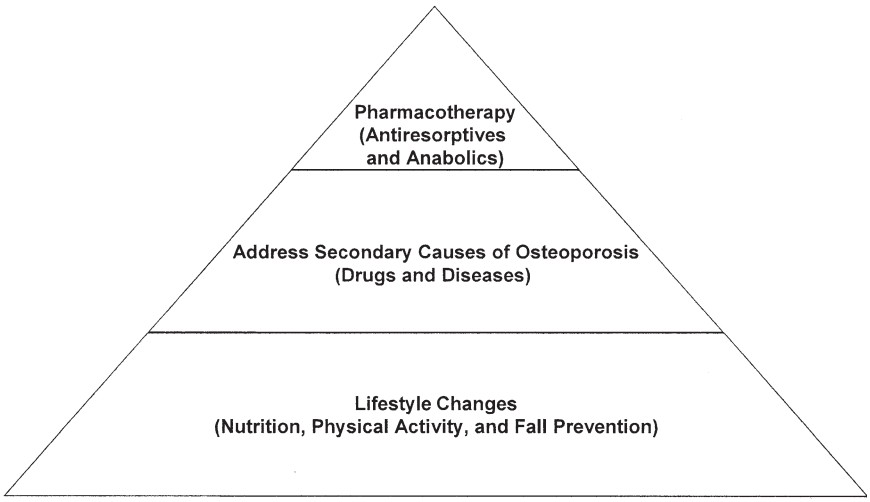

Figure 1 Pyramidal approach to treatment of bone disease. (Adapted from *Bone Health and Osteoporosis: A Report of the Surgeon General*.[2])

Table 4 Recommendations for calcium and vitamin D supplementation

	Use	Dosage
Calcium	Supplementation recommended for most men and women aged >50 yr	Total intake 1,000 to 1,500 mg/day (adjust dosage according to dietary calcium intake)
Vitamin D	Supplementation recommended for most men and women	Age 51 to 70 yr: 400 IU/day Age ≥70 yr: 600 IU/day In patients at risk for deficiency because of inadequate sunlight exposure: 800 IU/day

Adapted from *JAMA*,[1] *Menopause*,[11] and National Institutes of Health.[18,19]

goals, the US Surgeon General has recommended a pyramidal approach to treatment (**Figure 1**).[2] The base of the pyramid consists of lifestyle changes, including adequate calcium and vitamin D intake, physical activity, and fall prevention. The second level includes addressing and treating secondary causes of osteoporosis. The third level includes pharmacotherapeutic interventions to improve bone density and reduce the risk of fracture.

Physical Activity

Physical activity is necessary for bone formation and maintenance throughout life. Weight training has been shown to induce a small increase in BMD at some, but not all, skeletal sites.[13] Lower impact exercises, such as walking, have not been demonstrated to increase BMD or reduce fracture risk. Exercise-associated improvements in mobility, muscle function, and balance may also reduce fracture risk by decreasing the risk of falling.[14]

Nutrition and Calcium/Vitamin D Supplementation

Good nutrition and a balanced diet, with adequate calories, are important for normal growth. Adequate calcium intake is considered the most important lifestyle factor for attaining and maintaining adequate bone mass. Vitamin D is essential for the intestinal absorption of calcium; serum concentrations of 25-hydroxyvitamin D decline with age, necessitating supplementation in the majority of older women.[15] A double-blind, placebo-controlled study enrolled 301 healthy postmenopausal women, half of whom had a usual daily calcium intake of <400 mg/day; the other half had an intake of 400 to 650 mg/day.[16] Subjects were randomized to 2 years of therapy with placebo or calcium 500 mg/day, formulated as either calcium carbonate or calcium citrate malate. Although calcium supplementation did not affect bone loss from the spine in early postmenopausal women with low calcium intake, there were small gains in BMD at the femoral neck and radius and reductions in BMD loss at the spine among women who had been postmenopausal for ≥6 years and who had received calcium citrate malate. Calcium carbonate maintained BMD at the femoral neck and radius, but had no effect on spine BMD.[16] A second trial, conducted in healthy postmenopausal women who received calcium or placebo for 4 years (median intake, 640 mg/day at 4 years), found sustained, significant reductions in the rate of loss of total body BMD in

Table 5 Bisphosphonates

	Indication	Dosage*	Note for All Bisphosphonates
Alendronate†	Prevention and treatment of osteoporosis in postmenopausal women	Prevention: 5 mg/day or 35 mg/wk Treatment: 10 mg/day or 70 mg/wk	With all bisphosphonates, failure to follow dosing guidelines may result in increased risk of gastrointestinal side effects and suboptimal absorption; contraindicated in patients with swallowing abnormalities or who cannot remain upright after dosing
Ibandronate‡	Prevention and treatment of osteoporosis in postmenopausal women	Prevention and treatment 150 mg/mo	
Risedronate§	Prevention and treatment of osteoporosis in postmenopausal women	Prevention and treatment: 5 mg/day or 35 mg/wk	

*All bisphosphonates should be taken on an empty stomach, first thing in the morning, with 8 oz of water (no other liquid), ≥30 minutes before (ibandronate 1 hour before) eating or drinking. Patients should remain upright (sitting or standing) during this interval.

†Fosamax; Merck & Co., Inc., Whitehouse Station, NJ.

‡Boniva; Roche Laboratories, Inc., Nutley, NJ.

§Actonel; Aventis Pharmaceuticals, Inc., Kansas City, Mo.

Adapted from manufacturer prescribing information for individual drugs.[27,30,31]

the calcium group throughout the study period.[17] Significantly fewer fractures occurred in the calcium group compared with the placebo group.

Combining vitamin D supplementation with calcium has been shown to reduce risk of fracture. In a 3-year, double-blind study conducted in men and women aged ≥65 years, 389 subjects were randomized to calcium (500 mg/day) plus 700 international units (IU) of vitamin D_3.[15] Compared with placebo, combined therapy significantly increased BMD at the femoral neck and spine and over the total body. These differences were significant at 1 year; at 3 years, only total body BMD was significantly improved by calcium/vitamin D therapy. Furthermore, the incidence of nonvertebral fracture was significantly reduced among subjects who received active therapy.

The recommended dietary intake of calcium (**Table 4**) is 1,000 mg/day for men and women aged ≤50 years. For those >50 years, the recommended intake is 1,200 mg/day.[18] The current recommended dietary intake for vitamin D (Table 4) is 400 IU/day for men and women aged 51 to 70 years and 600 IU/day for those ≥71 years.[19] Women at risk for deficiency due to inadequate sunlight exposure should receive up to 800 IU/day.[11]

Fall Prevention and Bone Protection

Approximately 30% of people aged ≥60 years fall at least once a year, with an increase in incidence in people aged ≥80 years.[20] Falls have serious consequences in patients with osteoporosis or osteopenia; therefore, prevention of falls that can cause fractures should be a priority in older patients. All patients with osteoporosis or osteopenia should be assessed for risk factors for falls. These risk factors include previous falls, fainting or loss of consciousness, muscle weakness, dizziness or balance problems, impaired vision, and certain medications (e.g., sedatives, narcotic analgesics, anticholinergics, and antihypertensives). Environmental factors, such as obstacles and poor lighting, may also increase the risk of falls.[11] A safety checklist to help patients eliminate common household hazards may be found on the NOF Web site.[21] Hip protectors have been shown to reduce the risk of hip fracture for elderly patients who live in nursing homes; however, it remains unknown whether these findings can be generalized to lower risk populations.[22]

Pharmacologic Intervention

Bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin, teriparatide, and estrogen reduce the risk of fracture. It is important to note that the reductions in fracture afforded by these agents are in addition to the reductions obtained with calcium and vitamin D alone; in clinical trials of these agents, all patients—including those in the placebo groups—received calcium and vitamin D.

Bisphosphonates. Bisphosphonates are stable analogues of pyrophosphate that have a strong affinity for bone apatite; these agents inhibit bone resorption by reducing the recruitment and activity of osteoclasts and increasing apoptosis.[23–25] Bone formed while patients are receiving bisphosphonate treatment is histologically normal.[26]

Alendronate. Alendronate sodium (**Table 5**) is indicated for the prevention (5 mg daily and 35 mg weekly) and treatment (10 mg daily and 70 mg weekly) of osteoporosis in postmenopausal women.[27] According to the manufacturer's product information, it has been shown to increase bone mass and reduce the incidence of fractures of the hip and

spine in the treatment of preexisting osteoporosis. For the prevention of osteoporosis, alendronate should be considered in postmenopausal women who are at risk for osteoporosis and in whom maintenance of bone mass and reduction in risk of future fracture is needed. Alendronate is also indicated to increase bone mass in men, and to treat glucocorticoid-induced osteoporosis and Paget disease of bone in both men and women.[27]

The efficacy of alendronate 10 mg once daily in increasing bone mass was tested in 4 double-blind, placebo controlled clinical studies conducted in postmenopausal women with osteoporosis aged 44 to 84 years. These studies included 2 clinical 3-year trials of identical design, one of which was performed in the United States and the other multinationally.[27] In these studies, significant increases in BMD relative to baseline and placebo were observed at each measurement site; total body BMD also increased significantly. Two-year extension studies showed continued increases in BMD measured at the lumbar spine and trochanter, plus maintenance of BMD at the femoral neck, forearm, and total body.[27]

The effect of alendronate on fracture incidence was evaluated in the randomized, double-blind, placebo-controlled Fracture Intervention Trial (FIT).[28] Among patients with ≥1 baseline radiographic vertebral fracture, alendronate significantly reduced the risk of recurrent vertebral fracture, symptomatic vertebral fracture, hip fracture, and wrist fracture at 3 years. In a 4-year study conducted in patients with low bone mass but without a baseline radiographic vertebral fracture, alendronate resulted in significant reductions in risk of new vertebral fracture and any symptomatic fracture.[29] The risk of clinical vertebral fracture, hip fracture, or wrist fracture was not reduced significantly in this patient population. Similarly, in a combined analysis of the US and multinational 3-year studies (which included patients with or without baseline vertebral fracture), there was a statistically significant reduction in the proportion of patients treated with alendronate who had ≥1 vertebral fracture.[27] Among women ≥6 months postmenopausal, alendronate prevented bone loss in the majority of patients at the spine, hip, and total body and reduced the rate of bone loss at the forearm by approximately 50%.

Risedronate. Risedronate sodium (5 mg daily and 35 mg weekly) is indicated for the treatment and prevention of osteoporosis in postmenopausal women (Table 5).[30] For the treatment of osteoporosis, risedronate is indicated to increase BMD and reduce the incidence of vertebral fractures and a composite of nonvertebral osteoporosis-related fractures. For the prevention of osteoporosis, risedronate is indicated to maintain bone mass and reduce risk of fracture in women at risk for osteoporosis. Risedronate is also indicated for glucocorticoid-induced osteoporosis and Paget disease.[30]

To date, 4 studies have assessed the effect of risedronate on BMD: Daily risedronate yielded increases in BMD at the spine, hip, and wrist compared with placebo.[30] An additional study demonstrated the therapeutic equivalence of risedronate 35 mg once weekly in increasing BMD over 1 year.[30]

The efficacy of once-daily risedronate in reducing fracture was examined in 2 similar randomized, placebo-controlled, double-blind studies that enrolled approximately 4,000 postmenopausal women with radiographic evidence of previous vertebral fractures.[30] Treatment with once-daily risedronate resulted in significant reductions in the risk of new and worsening fractures together (33% to 49% relative risk reduction after 3 years) and new fractures alone (41% to 49% relative risk reduction after 3 years). In these trials, daily risedronate significantly reduced the incidence of nonvertebral osteoporosis-related fractures over 3 years (39% relative risk reduction) and reduced nonvertebral fracture incidence from 16% to 11%. When the studies were combined, there was an overall 36% reduction in relative risk. In a subanalysis of these studies, patients who received risedronate had a significantly smaller loss of height than in those who received placebo.[30]

Ibandronate. Ibandronate sodium (2.5 mg once daily or 150 mg once monthly) is indicated for the treatment and prevention of osteoporosis in postmenopausal women (Table 5).[31] In the treatment of osteoporosis, ibandronate is indicated to reduce the incidence of vertebral fractures. Ibandronate is also indicated to maintain bone mass and reduce the risk of fracture in postmenopausal women at risk for osteoporosis.[31]

The efficacy of ibandronate in treating postmenopausal osteoporosis was assessed in a randomized, double-blind, placebo-controlled study conducted in women with osteoporosis and 1 to 4 prevalent vertebral fractures.[31] Ibandronate was administered at dosages of 2.5 mg daily or 20 mg intermittently. The 2.5-mg dosage of daily ibandronate significantly reduced the incidence of new vertebral fracture by 52% compared with placebo, but it did not have an effect on nonvertebral osteoporotic fractures. Ibandronate was shown to significantly increase BMD at the lumbar spine, total hip, femoral neck, and trochanter compared with placebo; a later noninferiority study showed that ibandronate 150 mg once monthly was comparable to the 2.5 mg dosage in lumbar spine BMD achieved after 1 year of treatment.[31]

Bisphosphonate Dosing. The oral bioavailability of bisphosphonates is low, ranging from 1% to 3% of the ingested dose. When dosing recommendations are followed, the safety profile of bisphosphonates is generally favorable; mild gastrointestinal discomfort (e.g., dyspepsia, and abdominal pain) are the most common adverse events. Esophagitis has been reported with alendronate.[27] Of particular concern are the reports of osteonecrosis of the jaw among patients receiving bisphosphonates.[32] However, it should be noted that the majority of these patients (87%) were receiving high-dose bisphosphonates for indications other than osteoporosis (e.g., breast cancer, multiple myeloma) and were receiving intravenous therapy with either zoledronic acid (31%) or pamidronate (57%).[32]

Table 6 Raloxifene, teriparatide, and calcitonin

	Indications	Dosage	Notes
Raloxifene	Prevention and treatment of postmenopausal osteoporosis	60 mg/day	• May reduce risk of breast cancer; improves lipids • Associated with increased risk of deep vein thrombosis and pulmonary embolism
Teriparatide*	Treatment of osteoporosis in postmenopausal women at high risk for fracture	20 μg/day (subcutaneous injection)	• Teriparatide given to rats for most of their lifetime caused some rats to develop a form of bone cancer. • Use of the drug for >2 years not recommended
Calcitonin	Treatment of postmenopausal osteoporosis in women who have been menopausal for ≥5 yr	200 IU/day intranasally; alternate nostrils daily	• Generally safe; patients may experience rhinitis or epistaxis
Certain estrogens	Prevention of postmenopausal osteoporosis	Various doses and regimens	• Increased risk of thrombosis and stroke

*Forteo; Eli Lilly and Company, Indianapolis, IN.
Adapted from National Osteoporosis Foundation,[3] *JAMA*,[40] *Cancer Res Treat*,[41] Eli Lilly and Company,[44] *N Engl J Med*,[45] Novartis Pharmaceutical Corp.[46]

Bisphosphonates have unique and relatively complicated dosing requirements (Table 5); in order to achieve optimum absorption and tolerability, these guidelines must be followed closely. Patients should take their pill with a full glass of water and avoid food and beverages for ≥30 minutes after morning dosing. Importantly, patients must remain upright for ≥30 minutes (60 minutes in the case of ibandronate) and until after their first food of the day. Failure to follow these guidelines increases the risk of esophageal side effects and reduces absorption of the medication.[27,30,31]

Both alendronate and risedronate are available in once-weekly formulations that have efficacy and tolerability similar to that of the daily formulations.[33-35] Ibandronate is available as a monthly formulation that appears to have efficacy and tolerability similar to that of the daily formulation. Once-weekly or once-monthly regimens may improve compliance and persistence with medication by increasing convenience, reducing pill burden, and lowering dosing frequency.[36,37]

SERMs. Raloxifene (60 mg once daily) is the only SERM currently approved for the prevention and treatment of osteoporosis (**Table 6**). It acts as an estrogen agonist on bone and lipid metabolism and as an estrogen antagonist in the breast and endometrium.[38] Raloxifene is effective in preventing postmenopausal bone loss and reducing the risk of vertebral fractures by 30% in patients with prevalent vertebral fractures and 50% in patients without a prior vertebral fracture over 3 years.[39] Reduction of nonvertebral fractures has not been demonstrated.

Raloxifene is taken daily. Its nonskeletal effects include reductions in serum lipids and a 76% reduction in the risk of breast cancer in women with osteoporosis ($P < 0.001$).[40] Raloxifene increases the risk of deep vein thrombosis and pulmonary embolism to a similar extent as hormone therapy.[41]

Estrogen Therapy. Although hormone therapy increases bone mass and reduces the risk of fracture in low-risk postmenopausal women, increases in the risk for breast cancer, stroke, thrombotic events, and cardiovascular disease associated with the combined use of conjugated equine estrogens and medroxyprogesterone acetate outweigh its skeletal benefit (Table 6).[42,43] The effects of estrogen on fracture risk in women with osteoporosis have not been evaluated. Hormone therapy is not approved for the treatment of osteoporosis because the fracture data required by the US Food and Drug Administration (FDA) were never submitted.

Teriparatide. Teriparatide is a recombinant formulation of the first 34 N-terminal amino acids of parathyroid hormone that increases bone mass and improves bone microstructure. In a study of 1,637 postmenopausal women, a subcutaneous once-daily dosage of 20 μg teriparatide decreased the occurrence of new vertebral fractures in postmenopausal women by 65%.[44] Compared with placebo, teriparatide also resulted in a 53% reduction in the risk of new nonvertebral fracture after a mean of 18 months of therapy.[45]

Teriparatide is approved for administration as a once-daily 20-μg subcutaneous injection into the thigh or abdominal wall for ≤2 years (Table 6). Teriparatide is associated with only minor side effects, including nausea and headache. Hypercalcemia is usually mild and transient.[45] High

doses of teriparatide have been shown to cause osteosarcoma in rats; however, long-term clinical studies have not demonstrated an increased frequency of tumors in bone or other tissues in humans.[44]

Calcitonin. Calcitonin is a peptide produced by thyroid C cells that inhibits bone resorption by inhibiting osteoclast activity.[38] Salmon calcitonin is FDA-approved for the treatment of osteoporosis in women who have been postmenopausal for ≥5 years. It is usually delivered as a daily intranasal spray that provides 200 IU of the drug (Table 6). Although nasal calcitonin is approved for the treatment of osteoporosis, the effect of nasal calcitonin on fracture risk is not stated in its prescribing information.[46] One trial[47] showed that the intranasal formulation reduced vertebral fracture by 33% to 36%, but an effect on nonvertebral or hip fracture risk was not observed.[47,48] Calcitonin is generally considered safe, although some patients experience rhinitis and, rarely, epistaxis.[3]

SUMMARY

Osteoporosis is a major health threat. Fractures may have a profound impact on quality of life. Many patients who sustain a hip fracture do not regain full mobility, often requiring nursing home care. Postmenopausal women should therefore be screened for osteoporosis risk factors and have their BMD levels tested, if warranted, in accordance with current guidelines. Use of BMD assists physicians in diagnosing osteoporosis and in monitoring treatment effects.

Primary care providers are ideally placed to assess their patients' risk for fracture and to ensure that all patients receive care using the pyramidal approach. The data summarized here show that a variety of effective, well-tolerated treatments for osteoporosis provide fracture risk reduction over and above risk reduction with calcium and vitamin D alone. Two keys to reducing fracture rate are first to target treatment to patients who are at increased risk of fracture and then to develop strategies to improve treatment continuation rates.

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